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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/715,666	11/18/2003	Jian Jeffrey Chen	R0144B-REG	5342

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EXAMINER	
HABTE, KAHSAY	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 12/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/715,666	CHEN ET AL.	
	Examiner	Art Unit	
	Kahsay Habte, Ph. D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-21, 27-28 and 30-35* is/are allowed.

6)☒ Claim(s) *22-26 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/26/04&11/28/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-35 are pending.

Abstract

2. The abstract's content fails to enable the reader thereof, regardless of his or her degree of familiarity with the patent documents, to quickly ascertain the character of the subject matter covered by the technical disclosure and fails to include that which is new in the art to which the invention pertains. There is no utility for the compounds claimed (see below).

In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 29 is rejected under 35 U.S.C. 102(b) as being anticipated by Elliot et al. (US Pat. No. 4,025,510). Cited reference on columns 5-6 (EXAMPLE 3) discloses 2,4-Diphenyl-6-methylthio-4H-pyrimidino[4,5-e][1,3,4]thiadiazine compound that is the same as applicants when applicant's formula I has the following substituents:

X^1 = S; X^2 = a bond; Ar^1 = phenyl; R^7 = CH_3; R^3 = aryl; and n = 0.

Since said compound is the same as applicants, a 102(b) rejection is proper.

4. Claim 29 is rejected under 35 U.S.C. 102(b) as being anticipated by Elliot et al. {J. Heterocyclic Chem, (**1981**), pp 799-800, Vol. 189, No 4}. Cited reference on page 799 discloses 6-methylsulfonyl-4H-pyrimido[4,5-e][1,3,4]thiadiazine compound (compound 8) that is the same as applicants when applicant's formula I has the following substituents:

X^1 = S; X^2 = a bond; Ar^1 = phenyl; R^7 = CH_3; R^3 = H; and n = 2.

Since said compound is the same as applicants, a 102(b) rejection is proper.

5. Claim 29 is rejected under 35 U.S.C. 102(b) as being anticipated by Elliot et al. {Journal of Organic Chemistry (**1980**), 45(18), 3677-81}. Cited reference on page 3677 and page 3680 discloses compound **6a**: 2,4-Diphenyl-6-methylthio-4H-pyrimido[4,5-e][1,3,4]oxadiazine that is the same as applicants when applicant's formula I has the following substituents:

X^1 = O; X^2 = a bond; Ar^1 = phenyl; R^7 = CH_3; R^3 = aryl; and n = 0.

Since said compound is the same as applicants, a 102(b) rejection is proper.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22 and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of Crohn's disease, inflammatory bowel disease, rheumatoid arthritis or chronic obstructive pulmonary disease, does not reasonably provide enablement for the treatment of other forms of arthritis and adult respiratory distress syndrome (ARDS). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There has been recited a treatment of arthritis in general, but the specification is not enabled for such a scope. There are many types of arthritis (e.g. osteoarthritis, gouty arthritis, rheumatoid arthritis, systematic lupus erythematosus (SLE), juvenile arthritis, degenerative joint disease, psoriatic arthritis, Paget's disease, Reiter's syndrome, etc.) that are different in nature. Most of said arthritis operate in different mechanism. For example, gouty arthritis arises from an overproduction of uric acid, or a

reduced ability of the kidney to eliminate uric acid so that uric acid sodium salt builds up in joints. Rheumatoid arthritis is a chronic disease and it is an autoimmune disorder. Osteoarthritis is the most common form of arthritis and develops when cartilage wears out and bone rubs against bone. Cartilage contains fluid and elastic tissue, and reduces friction as the joint moves. Most often the weight-bearing joints, such as the hips, knees and spine, are affected by osteoarthritis. The mechanism of SLE is unknown. For example, or unknown mechanism

According to a recent article by Brown et al. {*Bioorg. Med. Chem. Lett. 14(2004) 5383-7*}, it has been disclosed that novel series of p38 MAP kinase inhibitors for the potential treatment of rheumatoid arthritis. There is no mention of p38 kinase inhibitors for the treatment of arthritis such as osteoarthritis, gouty arthritis, systematic lupus erythematosus, juvenile arthritis, degenerative joint disease, psoriatic arthritis, Paget's disease, or Reiter's syndrome. Thus, applicants are entitled for the treatment of rheumatoid arthritis, but not for the treatment of arthritis in general.

ARDS is a medical emergency. It can be caused by any major lung inflammation or injury. Some common causes include pneumonia, septic shock, trauma, aspiration of vomit, or chemical inhalation. ARDS develops as inflammation and injury to the lung and causes a buildup of fluid in the air sacs. This fluid inhibits the passage of oxygen from the air into the bloodstream. The fluid buildup also makes the lungs heavy and stiff, and the lungs' ability to expand is severely decreased. Blood concentration of oxygen

can remain dangerously low in spite of supplemental oxygen delivered by a mechanical ventilator (breathing machine) through an endotracheal tube (breathing tube). Typically patients require care in an intensive care unit (ICU). Symptoms usually develop within 24 to 48 hours of the original injury or illness. ARDS often occurs along with the failure of other organ systems, such as the liver or the kidneys. To this day, there is no pharmacological treatment for ARDS.

7. Claims 25-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of atherosclerosis, does not reasonably provide enablement for the treatment of restenosis and cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claim sets forth the treatment of cancer generally. However, there never has been a compound capable of treating cancer generally. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and

HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.
When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Restenosis, or recurrent stenosis, is an extremely general term. Stenosis is the narrowing of any canal, orifice, valve, duct, artery, vein, tube (such as trachea), opening, etc. in the body. These can arise from obstructive lesions, deposits of granulations, organ hypertrophy, etc. There is no such thing as being able to treat such widely diverse problems which arise from different sources.

8. Claims 22 and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention. In claim 24, a method of treating Alzheimer's disease has been recited, but the specification is not enabled for such a scope.

The central characteristic of Alzheimer's disease is the deficiency in the level of the neurotransmitter Acetylcholine that plays an important role in memory or it is believed that too much stimulation of nerve cells by glutamate may be responsible for the degeneration of nerves that occur in Alzheimer's disease. Like other neurotransmitters, glutamate is produced and released by nerve cells in the brain. The released glutamate then travels to nearby nerve cells where it attaches to a receptor on the surface of the cells called the N-methyl-D-aspartate (NMDA) receptor. Drugs such as memantine blocks the receptor and thereby decreases the effects of glutamate. It is thought that by blocking the NMDA receptor and the effects of glutamate, memantine may protect nerve cells from excess stimulation by glutamate. Thus, Alzheimer's disease can be treated by Acetylcholinesterase inhibitors that reduce the depletion of acetylcholine or by drugs that inhibit NMDA receptor. The skill level in the art is so low that the only treatments available to this day are drugs that inhibit Acetylcholinesterase or drugs that inhibit NMDA receptor that decreases the effects of glutamate. Applicants' compounds do not do this. Thus, the enablement rejection is proper.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 22 and 25, it has been recited a method of treating p38 MAP or FGFR kinase mediated disorders. The scope of claims 22 and 25 are unknown. Which diseases are these? Determining whether a given disease responds or does not respond to such mediator will surely involve undue experimentation. Suppose that a given inhibitor X when administered to a patient with Disease D does not obtain a response. Does one then conclude that Disease D does not fall within this claim? Keep in mind that:

A. It may be that the next patient will respond. It is quite common for pharmaceuticals to work only with some people, not all. Thus, how many need to be tested?

B. It may be that the wrong dosage or dosage regimen was employed. It is quite common for pharmaceuticals to work at one dosage, but not at another which is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? Thus, how many dosages and dosage regimens must be tried before one is certain that this pharmaceutical won't affect Disease D?

C. It may be that X simply isn't potent enough for Disease D, but that another inhibitor Y is potent enough, so that D really does fall within the claim. Thus, how many

different mediators must be tried before one concludes that D doesn't fall within the claim?

D. Conversely, if D responds to Y but not to X, can one really conclude that D falls within the claim? It may be that the X result is giving the accurate answer, and that the success of Y arises from some other unknown property which Y is capable of. Thus, when mixed results are obtained, how many more pharmaceuticals need be tested?

E. Finally, suppose that X really will work, but only when combined with Z. There are for example, agents in the antiviral and anticancer technology which are not themselves effective, but the disease will respond when the agents are combined with something else.

F. In addition, literally speaking, any disorder can be treated with any drug, although the treatment might not be successful. Assuming that "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000?

As a result, determining the true scope of the claim will involve extensive and potentially open-ended research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (571) 272-0667. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on (571) 272-0674, if there is no reply within 24 hours, James Wilson (Acting SPE) can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kahsay Habte, Ph. D.
Examiner
Art Unit 1624

Mark L. Berch
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KH
November 30, 2004